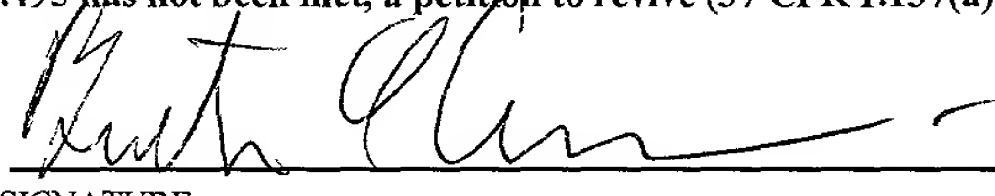


TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER  1581/00240
		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) <b>09/762215</b>
INTERNATIONAL APPLICATION NO.  PCT/JP00/03574	INTERNATIONAL FILING DATE  2 June 2000	PRIORITY DATE CLAIMED  4 June 1999
TITLE OF INVENTION Processes for the Preparation of 5-Hydroxy-3-Oxopentanoic Acid Derivatives		
APPLICANT(S) FOR DO/EO/US Nishiyama, Akira, Inoue, Kenji		
<p>Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:</p> <ol style="list-style-type: none"> <li><input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371</li> <li><input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. § 371.</li> <li><input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).</li> <li><input type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</li> <li><input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))             <ol style="list-style-type: none"> <li><input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</li> <li><input checked="" type="checkbox"/> has been transmitted by the International Bureau.</li> <li><input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> </li> <li><input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</li> <li><input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))             <ol style="list-style-type: none"> <li><input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</li> <li><input type="checkbox"/> have been transmitted by the International Bureau.</li> <li><input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li><input type="checkbox"/> have not been made and will not be made.</li> </ol> </li> <li><input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li><input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</li> <li><input type="checkbox"/> A translation of the Annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</li> </ol> <p>Items 11. to 16. below concern other document(s) or information included:</p> <ol style="list-style-type: none"> <li><input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li><input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li><input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> <li><input type="checkbox"/> A substitute specification</li> <li><input type="checkbox"/> A change of power of attorney and/or address letter</li> <li><input checked="" type="checkbox"/> Other items or information: International Search Report</li> </ol>		

U.S. APPLICATION NO (If known, see 37 CFR 1.5) <b>09/762215</b>		INTERNATIONAL APPLICATION NO. PCT/JP00/03574		ATTORNEY'S DOCKET NUMBER 1581/00240			
<input checked="" type="checkbox"/> The following fees are submitted:  <b>Basic National Fee (37 CFR 1.492(a)(1)-(5)):</b> Search Report has been prepared by the EPO or JPO.....\$860.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) .....\$690.00 No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....\$760.00  Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....\$1,000.00  International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) .....\$100.00				CALCULATIONS		PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$860			
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$			
Claims	Number Filed	Number Extra	Rate				
Total Claims	20- 20 =	0	X \$18.00	\$			
Independent Claims	3- 3 =	0	X \$80.00	\$			
Multiple dependent claim(s)(if applicable)			+ \$270.00	\$			
TOTAL OF ABOVE CALCULATIONS =				\$860			
Reduction by 1/2 for filing by small entity, if applicable.				\$			
SUBTOTAL =				\$860			
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$			
TOTAL NATIONAL FEE =				\$860			
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$			
TOTAL FEES ENCLOSED =				\$860			
				Amount to be:			
				refunded \$			
				charged \$			
a. <input checked="" type="checkbox"/> A check in the amount of \$860 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. <u>22-0185</u> in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>22-0185</u> . A duplicate copy of this sheet is enclosed.							
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status SEND ALL CORRESPONDENCE TO: <b>Connolly Bove Lodge &amp; Hutz LLP</b> 1990 M Street, N.W., Suite 800 Washington, DC 20036-3425							
SIGNATURE  NAME Burton A. Amernick 24,852 REGISTRATION NUMBER							

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: :  
: Akira Nishiyama et al. :  
Serial No.: To be assigned : Art Unit: To be assigned  
Filed: Herewith : Examiner: To be assigned  
For: Processes for the Preparation of : Atty Docket: 1581/00240  
5-Hydroxy-3-Oxopentanoic :  
Acid Derivatives :  
:

PRELIMINARY AMENDMENT

Commissioner for Patents  
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-captioned case as follows.

IN THE CLAIMS

Please amend the claims as follows.

Claim 3, line 1, delete "or 2".

Claim 4, line 1, delete "2 or 3".

Claim 8, line 1, delete "or 7".

Claim 9, line 1, delete "7 or 8".

Claim 12, line 1, delete "or 11".

Claim 13, line 1, delete "11 or 12".

Claim 14, line 1, delete "any of Claims 1 to 13" and insert ---Claim 1---.

Claim 15, line 1, delete "any of Claims 1 to 14" and insert ---Claim 1---.

Claim 16, line 1, delete "any of Claims 1 to 13" and insert ---Claim 1---.

Claim 17, line 1, delete "any of Claims 1 to 16" and insert ---Claim 1---.

Please add the following new claims.

18. The process according to Claim 2

wherein, referring to the acetic acid ester, R<sup>1</sup> represents a tert-butyl group.

19. The process according to Claim 2

wherein a magnesium halide is added in permitting the lithium amide to act.

20. The process according to Claim 3

wherein a magnesium halide is added in permitting the lithium amide to act.

### REMARKS

The claims have been amended to eliminate multiple dependency and to improve their format. None of these amendments is believed to involve any new matter. Accordingly, it is respectfully requested that the foregoing amendments be entered, that the application as so amended receive an examination on the merits, and that the claims as now presented receive an early allowance.

Respectfully submitted,



Burton A. Amernick (24,852)

Connolly Bove Lodge & Hutz LLP

1990 M Street, N.W., Suite 800

Washington, D.C. 20036-3425

Telephone: 202-331-7111

Date: 2-05-01

## SPECIFICATION

## PROCESSES FOR THE PREPARATION OF 5-HYDROXY-3-OXOPENTANOIC ACID DERIVATIVES

5

## TECHNICAL FIELD

The present invention relates to a process for producing a 5-hydroxy-3-oxopentanoic acid derivative which is of value as a pharmaceutical intermediate, particularly an intermediate of an HMG-CoA reductase inhibitor.

10

## BACKGROUND ART

The hitherto-known process for producing a 5-hydroxy-3-oxopentanoic acid derivative includes the following processes.

15

(1) The process in which 3-hydroxypropionic acid imidazolide prepared from 3-hydroxypropionic acid and diimidazolyl ketone is coupled to a malonic acid monoester monomagnesium salt (Synthesis, 1992, 4, 403-408).

20

(2) The process in which a lithium enolate prepared from tert-butyl acetate and lithium diisopropylamide is reacted with a 3-hydroxypropionic acid ester (Japanese Kokai Publication Hei-8-198832, Chem. Pharm. Bull., 1994, 42 (11), 2403-2405, Tetrahedron Lett., 1993, 49 (10), 1997-2010, Tetrahedron, 1990, 46 (29), 7283-7288, Tetrahedron Asymmetry, 1990, 1 (5), 307-310, Tetrahedron Lett., 1989, 30 (38), 5115-5118, Tetrahedron Lett., 1987, 28 (13), 1385-1388, Synthesis, 1985, (1), 45-48).

25

However, the prior art (1) requires an expensive starting material while the prior art (2) involves a very low reaction temperature of -78 °C to -40 °C, so that neither is a favorable process for commercial-scale production.

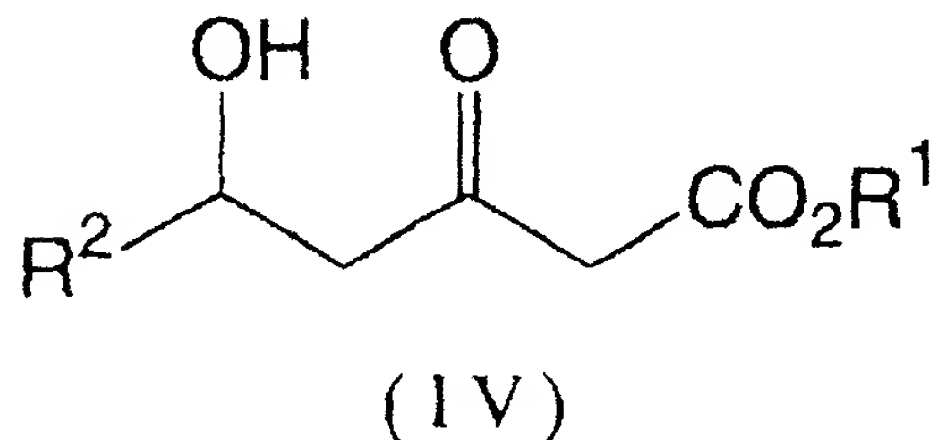
30

## DISCLOSURE OF INVENTION

The object of the present invention, in the above perspective, is to provide a production process by which a

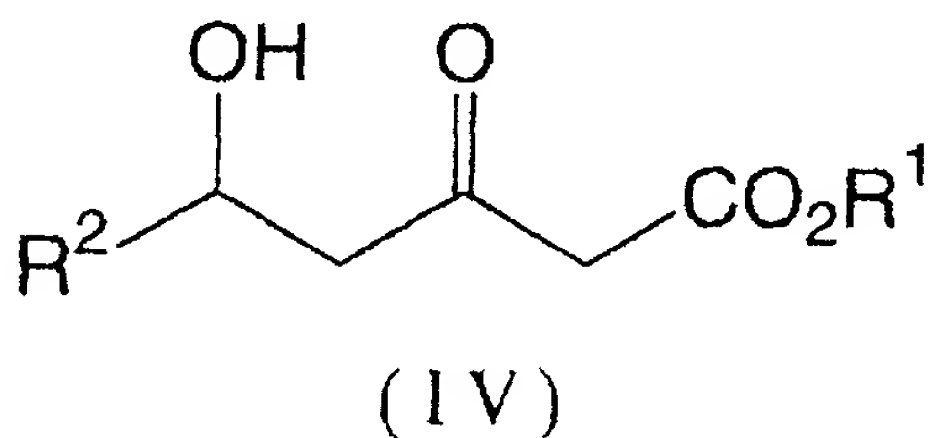
35

5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV), a useful pharmaceutical intermediate, can be prepared easily from a readily available, inexpensive starting material without using any extraordinary production equipment such as a very-low-temperature reactor:



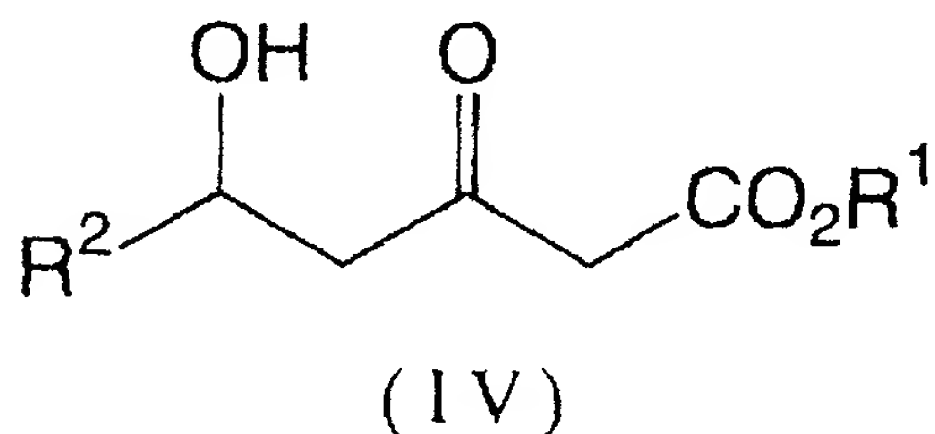
wherein R<sup>1</sup> represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R<sup>2</sup> represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group.

The inventors of the present invention made intensive investigations in view of the above state of the art and found that, starting with a readily available, inexpensive starting material, a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV) can be produced without using any special equipment such as a very-low-temperature reactor:



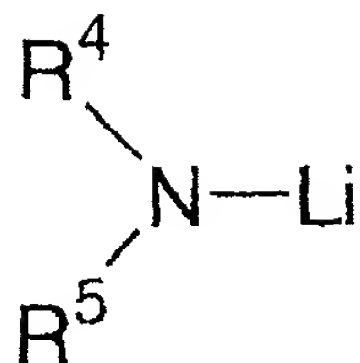
wherein  $R^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $R^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent,  
 5 an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group.

- 10 The present invention, therefore, relates to a process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



- 15 wherein  $R^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $R^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a  
 20 substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

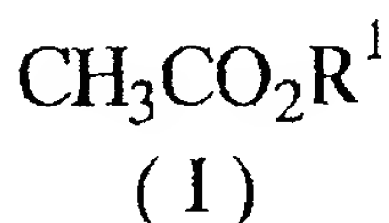
- 25 which comprises permitting a lithium amide of the following formula (III):



(III)

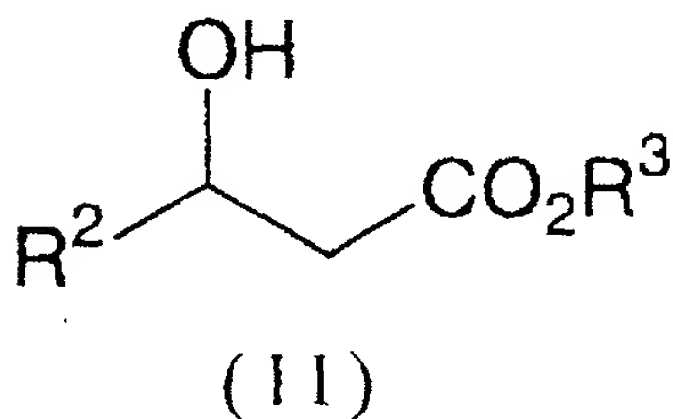
5 wherein R<sup>4</sup> and R<sup>5</sup> may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms, and a silyl group

to act upon a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II) at a temperature not below -20 °C:



10

wherein R<sup>1</sup> represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



15

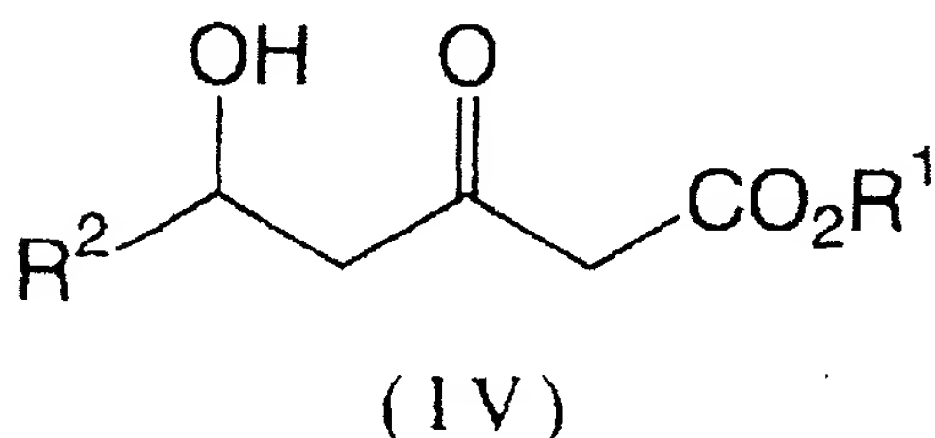
wherein R<sup>2</sup> represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group;

20



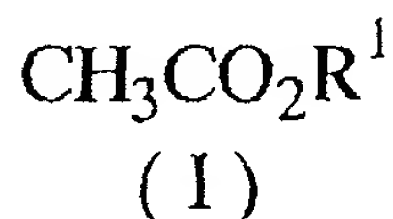
$R^3$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $R^2$  and  $R^3$  may be joined to each other to form a ring.

- 5        The invention further relates to a process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):

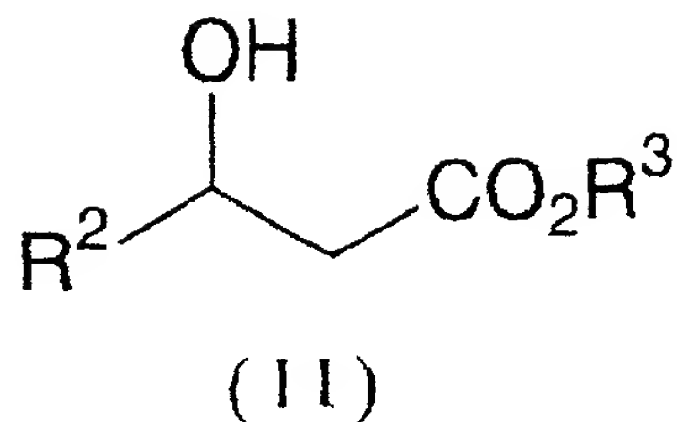


- 10        wherein  $R^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $R^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

- 15        which comprises treating a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II):

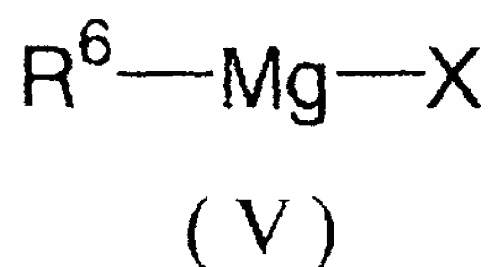


- 20        wherein  $R^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:

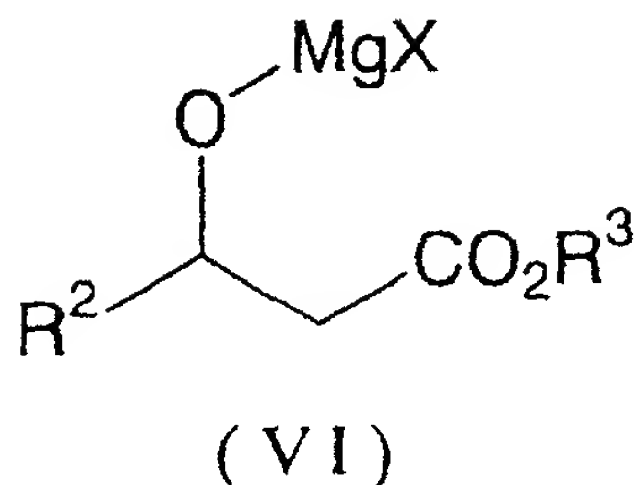


- wherein  $\text{R}^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group;  $\text{R}^3$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $\text{R}^2$  and  $\text{R}^3$  may be joined to each other to form a ring

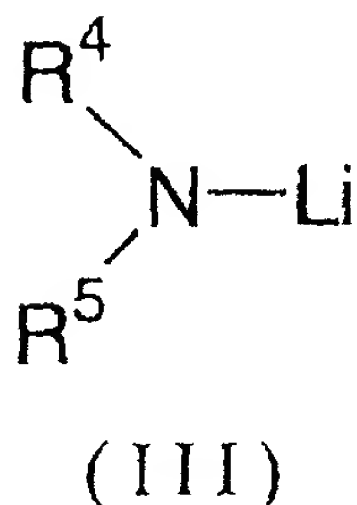
with a Grignard reagent of the following formula (V):



- wherein  $\text{R}^6$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and X represents a halogen atom to prepare a mixture of a compound of the following formula (VI) and an acetic acid ester of the above formula (I):

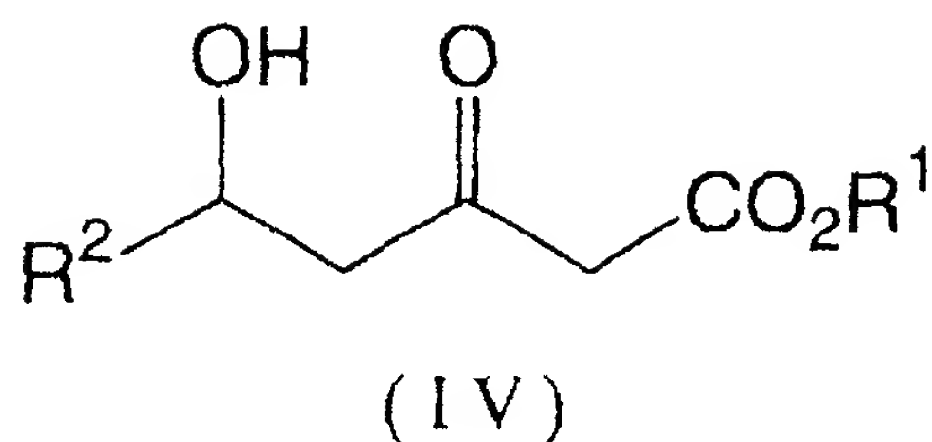


- wherein  $\text{R}^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group;  $\text{R}^3$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms;  $\text{R}^2$  and  $\text{R}^3$  may be joined to each other to form a ring; and X represents a halogen atom,
- and permitting a lithium amide of the following formula (III):



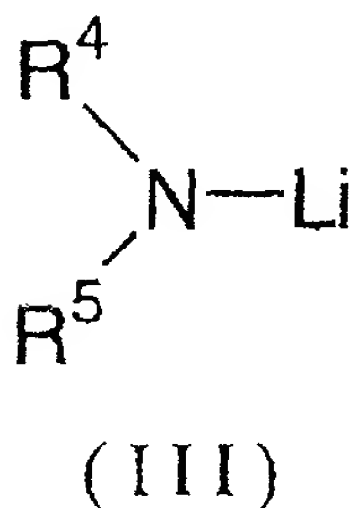
- wherein  $\text{R}^4$  and  $\text{R}^5$  may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms, and a silyl group,
- to act upon the mixture at a temperature not below  $-20^\circ\text{C}$ .

The present invention further relates to a process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



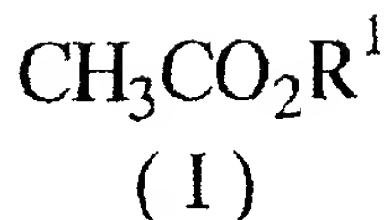
wherein  $\text{R}^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $\text{R}^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

which comprises permitting a lithium amide of the following formula (III):



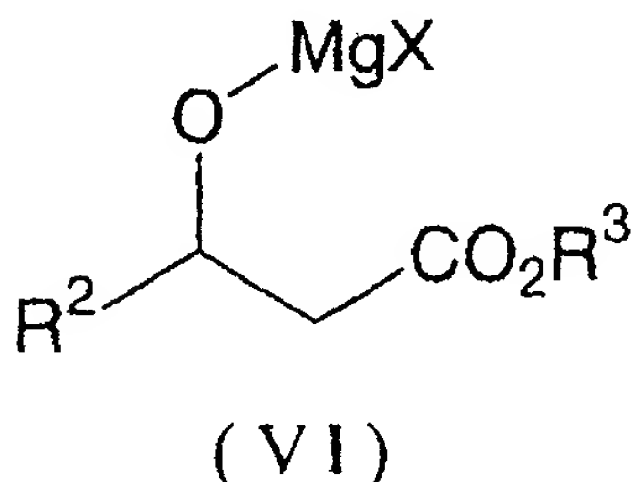
wherein  $\text{R}^4$  and  $\text{R}^5$  may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a compound of the following formula (VI) at a temperature not below  $-20^\circ\text{C}$ :



wherein  $\text{R}^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:

5

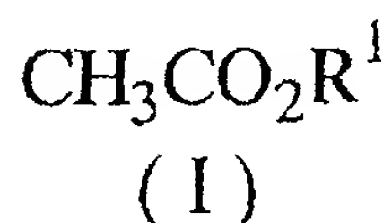


wherein  $\text{R}^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group;  $\text{R}^3$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms;  $\text{R}^2$  and  $\text{R}^3$  may be joined to each other to form a ring; and X represents a halogen atom.

The present invention is now described in detail.

The acetic acid ester is represented by the general formula (I):

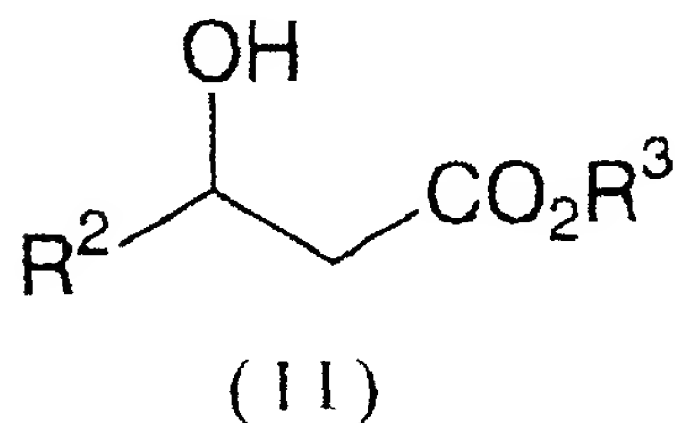
20



Here,  $\text{R}^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms. As specific examples, there can be

mentioned methyl, ethyl, isopropyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, benzyl, and p-nitrobenzyl, among others. Preferred is t-butyl.

The 3-hydroxypropionic acid derivative is represented by  
5 the general formula (II):



Here,  $\text{R}^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl  
10 group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxy carbonyl group. As specific examples, there can be  
15 mentioned methyl, ethyl, isopropyl, tert-butyl, chloromethyl, bromomethyl, cyanomethyl, benzyloxymethyl, trityloxymethyl, tert-butyldiphenylsilyloxymethyl, dimethoxymethyl, 1,3-dithian-2-yl, 1,3-dithiolan-2-yl, vinyl, 2-phenylvinyl, 2-phenylethyl, 2-carbobenzyloxyaminoethyl, phenyl, naphthyl,  
20 p-methoxyphenyl, benzyl, p-nitrobenzyl, cyano, carboxy and tert-butoxycarbonyl, among others. Preferred are methyl, ethyl, isopropyl, tert-butyl, chloromethyl, cyanomethyl, benzyloxymethyl, trityloxymethyl, tert-butyldiphenylsilyloxymethyl, dimethoxymethyl, vinyl, 2-  
25 phenylethyl, phenyl, naphthyl, p-methoxyphenyl, benzyl and p-nitrobenzyl, among others. More preferred are chloromethyl, cyanomethyl and benzyloxymethyl.

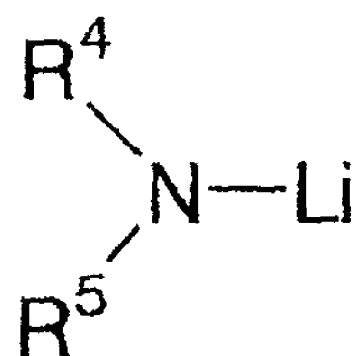
As the substituents on the alkyl, alkenyl, aryl and aralkyl groups each represented by the above  $\text{R}^2$ , there can be  
30 mentioned halogen, cyano,  $\text{C}_{7-19}$  aralkyloxy,  $\text{C}_{1-12}$  alkoxy,  $\text{C}_{6-12}$  aryl,

nitro, siloxy, N-protected amino, C<sub>1-12</sub> alkylthio, C<sub>6-12</sub> arylthio and C<sub>7-12</sub> aralkylthio, among others. The number of substituents may be 0 to 3. The number of carbon atoms of said alkoxycarbonyl group in the above R<sup>2</sup> may for example be 2 to 13.

- 5 R<sup>3</sup> represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms. Specifically, methyl, ethyl, isopropyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, benzyl, p-nitrobenzyl, etc. can be mentioned. Preferred is  
10 methyl or ethyl.

R<sup>2</sup> and R<sup>3</sup> may be joined to each other to form a ring; R<sup>2</sup> and R<sup>3</sup> specifically may jointly represent a methylene group, an ethylene group, a propylene group or the like, preferably a methylene group.

- 15 The lithium amide is represented by the general formula (III):



(III)

- Here, R<sup>4</sup> and R<sup>5</sup> may be the same or different and each  
20 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms, and a silyl group. Specifically, there can be mentioned methyl, ethyl, isopropyl, tert-butyl, cyclohexyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, benzyl, p-  
25 nitrobenzyl, trimethylsilyl, triethylsilyl and phenyldimethylsilyl, among others. Preferred is isopropyl.

The Grignard reagent is represented by the general formula (V):



(V)

Here,  $R^6$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms. Specifically, there can be mentioned  
 5 methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, benzyl and p-nitrobenzyl, among others. Preferred are methyl, ethyl, isopropyl, n-butyl, tert-butyl, etc. More preferred is tert-butyl. X represents a halogen atom. Preferred are chloro,  
 10 bromo and iodo. More preferred is chloro.

The process for producing a 5-hydroxy-3-oxopentanoic acid derivative in accordance with the present invention is now described.

When a reaction involving an enolate such as an  
 15 acetate-derived enolate is conducted at a non-very-low reaction temperature, for example not below  $-20^{\circ}\text{C}$ , the self-condensation of the enolate proceeds predominantly to remarkably sacrifice the rate of conversion of the objective reaction. However, in the process developed by the present inventors, the self-  
 20 condensation of the acetic enolate can be minimized so that the objective reaction can be carried out in high yield.

Thus, this reaction is carried out by adding a solution of a lithium amide dropwise to a mixed solution of an acetic acid ester and a 3-hydroxypropionic acid derivative. The  
 25 acetic acid ester is not particularly restricted but includes, for example, methyl acetate, ethyl acetate, isopropyl acetate, t-butyl acetate, phenyl acetate and benzyl acetate. Preferred is t-butyl acetate. The amount of use of this acetic acid ester is preferably 1 to 5 molar equivalents, and more preferably 1.5  
 30 to 3 molar equivalents, based on the 3-hydroxypropionic acid derivative. The 3-hydroxypropionic acid derivative is not particularly restricted but includes methyl 3-



hydroxypropionate, ethyl 3-hydroxybutanoate, ethyl 3-hydroxypentanoate, ethyl 4-chloro-3-hydroxybutanoate, ethyl 4-bromo-3-hydroxybutanoate, 4-cyano-3-hydroxybutanoate, ethyl 4-benzyloxy-3-hydroxybutanoate, ethyl 4-trityloxy-3-hydroxybutanoate, ethyl 4-tert-butyl diphenyloxy-3-hydroxybutanoate, ethyl 3-cyano-3-hydroxypropionate, methyl 4,4-dimethoxy-3-hydroxybutanoate, ethyl 5-phenyl-3-hydroxyhexanoate, ethyl 5-carbobenzyloxyamino-3-hydroxyhexanoate, phenyl 3-phenyl-3-hydroxypropionate, methyl 3-naphthyl-3-hydroxypropionate, benzyl 4-phenyl-3-hydroxybutanoate, ethyl 4-p-nitrophenyl-3-hydroxybutanoate and 3-hydroxybutyrolactone, among others.

Furthermore, in accordance with the present invention, an optically active 3-hydroxypropionic acid derivative can be used as the starting material to give the corresponding objective compound without being sacrificed in optical purity. Therefore, more preferred are optically active ethyl 3-hydroxybutanoate, ethyl 4-chloro-3-hydroxybutanoate, ethyl 4-cyano-3-hydroxybutanoate, ethyl 4-benzyloxy-3-hydroxybutanoate, and 3-hydroxybutyrolactone, among others.

These optically active 3-hydroxypropionic acid derivatives can be easily prepared in accordance with the known production processes. For example, (3S)-4-chloro-3-hydroxybutyric acid ethyl ester can be produced by the process described in WO 98/35025; (3S)-4-cyano-3-hydroxybutyric acid ethyl ester can be produced by the process disclosed in Japanese Kohyo Publication Hei-7-500105; and (S)-3-hydroxybutyrolactone can be produced by the process described in Synthetic Communication 16, 183, 1986.

The lithium amide is not particularly restricted but includes lithium dimethylamide, lithium diethylamide, lithium diisopropylamide, lithium di-tert-butylamide, lithium dicyclohexylamide, lithium 2,2,6,6-tetramethylpiperidine, lithium diphenylamide, lithium dibenzylamide and lithium hexamethyldisilazide, among others. Preferred is lithium

diisopropylamide. These can be used each alone or two or more of them can be used in combination. The amount of use of the lithium amide relative to the 3-hydroxypropionic acid derivative is preferably 1 to 10 molar equivalents, more preferably 2 to 5 molar equivalents.

The yield of the objective compound can be increased by conducting this reaction in the presence of a magnesium halide. Thus, the reaction can be conducted with greater advantage by adding a solution of a lithium amide to a mixed solution containing the acetic acid ester, 3-hydroxypropionic acid derivative and magnesium halide. The magnesium halide is not particularly restricted but includes, for example, magnesium chloride, magnesium bromide and magnesium iodide. Preferred is magnesium chloride. The amount of use of the magnesium halide relative to the 3-hydroxypropionic acid derivative is preferably 0.5 to 10 molar equivalents, more preferably 1 to 5 molar equivalents.

Referring, further, to this reaction, the yield of the objective compound can be further improved by treating the 3-hydroxypropionic acid derivative with a Grignard reagent in advance to prepare the halomagnesium alkoxide compound and, then, conducting the reaction. In this case, the Grignard reagent is added dropwise to the 3-hydroxypropionic acid derivative to prepare the halomagnesium alkoxide compound and, after mixing the acetic acid ester, the lithium amide solution is added dropwise to carry out the reaction. As an alternative, the treatment with the Grignard reagent may be carried out in the presence of the acetic acid ester. Thus, the reaction can be conducted by adding the Grignard reagent to a mixed solution containing the acetic acid ester and 3-hydroxypropionic acid derivative and, then, adding the lithium amide solution dropwise to the reaction mixture. This Grignard reagent is not particularly restricted but includes for example methylmagnesium bromide, ethylmagnesium iodide, isopropylmagnesium chloride, n-butylmagnesium chloride and

tert-butylmagnesium chloride. Preferred is tert-butylmagnesium chloride. The amount of use of the Grignard reagent relative to the 3-hydroxypropionic acid derivative is preferably 0.5 to 5 molar equivalents. More preferred is 1 to 5 2 molar equivalents.

The solvent which can be used for this reaction may for example be an aprotic organic solvent. The organic solvent mentioned above includes hydrocarbon solvents such as benzene, toluene, n-hexane, cyclohexane, etc.; ether solvents such as 10 diethyl ether, tetrahydrofuran, 1,4-dioxane, methyl t-butyl ether, dimethoxymethane, ethylene glycol dimethyl ether, etc.; halogen-containing solvents such as methylene chloride, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; and aprotic polar solvents such as dimethylpropyleneurea, 15 N-methylpyrrolidone, hexamethylphosphoric triamide, etc., among others. These solvents may be used each alone or two or more of them may be used in a suitable combination. Preferred, among the above-mentioned solvents, are hydrocarbon solvents, such as benzene, toluene, n-hexane, cyclohexane, etc., and 20 ether solvents, such as diethyl ether, tetrahydrofuran, 1,4-dioxane, methyl t-butyl ether, dimethoxymethane, ethylene glycol dimethyl ether and so on.

The reaction temperature for this reaction is preferably -20 °C to 80 °C. More preferred is -10 °C to 40 °C.

25 The aftertreatment of this reaction may be the routine aftertreatment for recovery of the reaction product from a reaction mixture. A typical procedure may comprise blending the reaction mixture at completion of the reaction with an aqueous solution of the common inorganic or organic acid, such 30 as hydrochloric acid, sulfuric acid, nitric acid, acetic acid and citric acid, and carrying out an extraction with the common extractant such as ethyl acetate, diethyl ether, methylene chloride, toluene and hexane. From the extract obtained, the reaction solvent and extractant are distilled by heating under 35 reduced pressure, for instance, whereby the objective product

can be isolated. The objective product thus obtained can be purified by the routine technique, such as crystallization, fractional distillation, column chromatography and/or the like to further enhance its purity.

5

#### BEST MODE FOR CARRYING OUT THE INVENTION

The following examples illustrate the present invention in further detail without defining its metes and bounds.

#### 10 Example 1 Tert-butyl 6-benzyloxy-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 5.01 g (49.5 mmol) of diisopropylamine and 5 mL of tetrahydrofuran was added dropwise to 30 mL (45 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 °C and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 8.0 ml of tetrahydrofuran were dissolved 2.38 g (10 mmol) of ethyl 4-benzyloxy-3-hydroxybutyrate and 2.32 g (20 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 °C. To this solution, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes, and the mixture was further stirred at 5 to 20 °C for 16 hours.

In a separate vessel, 35 mL of 3 N-hydrochloric acid was mixed with 30 mL of ethyl acetate under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 4:1) to give 1698 mg of tert-butyl 6-brenzyloxy-5-hydroxy-3-oxohexanoate (yellow oil) in 55% yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz/ppm): 1.46 (9H, s), 2.75 (2H, d), 2.93 (1H, bs), 3.39 (2H, s), 3.47 (2H, m), 4.28 (1H, m), 4.55 (2H, s), 7.29-7.36 (5H, m)

$^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 400 MHz/ppm): 27.9, 46.1, 51.1, 66.6, 73.1, 73.3, 82.1, 127.7, 127.8, 128.4, 137.8, 166.1, 203.0

Example 2 Tert-butyl 6-benzyloxy-5-hydroxy-3-oxohexanoate

5 Under argon gas, a solution composed of 3.90 g (38.5 mmol) of diisopropylamine and 3 mL of tetrahydrofuran was added dropwise to 22.9 mL (35 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 °C and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

10 In 3.0 ml of tetrahydrofuran were dissolved 2.38 g (10 mmol) of ethyl 4-benzyloxy-3-hydroxybutyrate and 2.32 g (20 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 °C. To this solution was added 5.7 g (10 mmol) of a solution of tert-butylmagnesium chloride

15 in toluene/tetrahydrofuran (1:2.5 by weight) (1.75 mol/kg) dropwise over 10 minutes, and the mixture was further stirred at 5 °C for 50 minutes. To this, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes, and the mixture was further stirred at 5 to 20 °C for 16 hours.

20 In a separate vessel, 30 mL of 3 N-hydrochloric acid was mixed with 30 mL of ethyl acetate under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The

25 solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 4:1) to give 2420 mg of tert-butyl 6-brenzyloxy-5-hydroxy-3-oxohexanoate (red oil) in 79% yield.

30

Example 3 Tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 2.67 g (26.4 mmol) of diisopropylamine and 5 mL of tetrahydrofuran was added dropwise to 15 mL (24 mmol) of n-butyllithium/hexane (1.6 mol/L)

35 with stirring at 5 °C and the mixture was stirred for 1 hour

to prepare a lithium diisopropylamide solution.

In 5.0 ml of tetrahydrofuran were dissolved 1.0 g (6.0 mmol) of ethyl (3S)-4-chloro-3-hydroxybutyrate and 2.78 g (24 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 °C. To this the lithium diisopropylamide solution prepared above was added dropwise over 20 minutes, and the mixture was further stirred at 5 to 20 °C for 16 hours.

In a separate vessel, 6.31 g of concentrated hydrochloric acid, 20 g of water, and 20 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 4:1) to give 86 mg of tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate (colorless oil) in 6% yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz/ppm): 1.48 (9H, s), 2.84 (1H, dd), 2.91 (1H, dd), 3.05 (1H, bs), 3.41 (2H, s), 3.55-3.64 (2H, m), 4.28-4.36 (1H, m)

#### Example 4 Tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 10.0 g (99 mmol) of diisopropylamine and 20 mL of tetrahydrofuran was added dropwise to 56.3 mL (90 mmol) of n-butyllithium/hexane (1.6 mol/L) with stirring at 5 °C and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 10.0 ml of tetrahydrofuran were suspended 3.0 g (18.0 mmol) of ethyl (3S)-4-chloro-3-hydroxybutyrate, 5.22 g (45 mmol) of tert-butyl acetate and 6.86 g (72 mmol) of magnesium chloride, and the suspension was stirred in an argon atmosphere at 0 to 5 °C. To this solution, the lithium diisopropylamide solution prepared above was added dropwise over 1 hour, and the

mixture was further stirred at 25 °C for 3 hours.

In a separate vessel, 21.7 g of concentrated hydrochloric acid, 30 g of water, and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was washed with water twice and the solvent was distilled off under reduced pressure to give 5.62 g of a red oil containing tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate.

This oil was analyzed by high-performance liquid chromatography (column: Nacalai Tesque, Cosmosil 5CN-R (4.6 mm × 250 mm), eluent: water/acetonitrile = 9/1, flow rate: 1.0 ml/min, detection: 210 nm, column temperature: 40 °C). The reaction yield was 65%.

#### 15 Example 5 Tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 26.71 g (264 mmol) of diisopropylamine and 18.8 g of tetrahydrofuran was added dropwise to 150 mL (240 mmol) of n-butyllithium/hexane (1.6 mol/L) with stirring at 5 °C and the mixture was stirred to prepare a lithium diisopropylamide solution.

In 20 mL of tetrahydrofuran were dissolved 12.5 g (75 mmol) of ethyl (3S)-4-chloro-3-hydroxybutyrate and 17.4 g (150 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 °C. To this solution was added 42.9 g (75 mmol) of a solution of tert-butyilmagnesium chloride in toluene/tetrahydrofuran (1:2.5, by weight) (1.8 mol/kg) dropwise over 30 minutes, and the mixture was further stirred at 5 °C for 30 minutes. Then, the lithium diisopropylamide solution prepared above was added dropwise over 3 hours and the mixture was further stirred at 5 °C for 16 hours.

In a separate vessel, 60.38 g of concentrated hydrochloric acid, 31.3 g of water, and 50 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with water twice and the solvent was distilled



off under reduced pressure to give 22.0 g of a red oil containing tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate.

The reaction yields as analyzed by the method described in Example 3 was 78%.

5

Example 6 Tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 5.01 g (49.5 mmol) of diisopropylamine and 5 mL of tetrahydrofuran was added dropwise to 30 mL (45 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 °C and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 8.0 mL of tetrahydrofuran were suspended 1.57 g (10 mmol) of ethyl (3S)-4-cyano-3-hydroxybutyrate and 2.32 g (20 mmol) of tert-butyl acetate, and the suspension was stirred in an argon atmosphere at 0 to 5 °C. To this solution, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes, and the mixture was further stirred at 5 to 20 °C for 16 hours.

In a separate vessel, 35 mL of 3 N-hydrochloric acid was mixed with 30 mL of ethyl acetate under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 3:1) to give 586 mg of tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate (red oil) in 26% yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz/ppm): 1.48 (9H, s), 2.61 (2H, m), 2.90 (2H, m), 3.42 (3H, s), 4.41 (1H, m)

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 400 MHz/ppm): 25.0, 28.0, 48.0, 50.9, 63.6, 82.8, 117.0, 166.0, 202.8

Example 7 Tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 5.01 g (49.5 mmol)



of diisopropylamine and 5 mL of tetrahydrofuran was added dropwise to 30 mL (45 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 °C and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

- 5 In 8.0 mL of tetrahydrofuran were suspended 1.57 g (10 mmol) of ethyl (3S)-4-cyano-3-hydroxybutyrate, 2.32 g (20 mmol) of tert-butyl acetate and 2.86 g (30 mmol) of magnesium chloride, and the suspension was stirred in an argon atmosphere at 0 to 5 °C. To this solution, the lithium diisopropylamide solution  
10 prepared above was added dropwise over 30 minutes, and the mixture was further stirred at 5 to 20 °C for 16 hours.

- In a separate vessel, 35 mL of 3 N-hydrochloric acid was mixed with 30 mL of ethyl acetate under stirring and the above reaction mixture was poured. After standing, the organic layer  
15 was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

- The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate =  
20 3:1) to give 1041 mg of tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate (red oil) in 46% yield.

#### Example 8 Tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate

- Under argon gas, a solution composed of 3.90 g (38.5 mmol)  
25 of diisopropylamine and 3 mL of tetrahydrofuran was added dropwise to 22.9 mL (35 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 °C and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

- In 3.0 mL of tetrahydrofuran were dissolved 1.57 g (10  
30 mmol) of ethyl (3S)-4-cyano-3-hydroxybutyrate and 2.32 g (20 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 °C. To this solution was added 5.7 g (10 mmol) of a solution of tert-butylmagnesium chloride in toluene/tetrahydrofuran (1:2.5, by weight) (1.75 mol/kg)  
35 dropwise over 10 minutes, and the mixture was further stirred

at 5 °C for 50 minutes. Then, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes and the mixture was further stirred at 5 to 20 °C for 16 hours.

In a separate vessel, 30 mL of 3 N-hydrochloric acid and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 3:1) to give 1302 mg of tert-butyl (5S)-6-cyano-5-hydroxy-3-oxohexanoate (red oil) in 57% yield.

15

#### Example 9 Tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate

Under argon gas, a solution composed of 5.01 g (49.5 mmol) of diisopropylamine and 5 mL of tetrahydrofuran was added dropwise to 30 mL (45 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 °C and the mixture was stirred for 1 hour to prepare a lithium diisopropylamide solution.

In 8.0 mL of tetrahydrofuran were suspended 1.02 g (10 mmol) of (3S)-3-hydroxybutyrolactone and 2.32 g (20 mmol) of tert-butyl acetate, and the suspension was stirred in an argon atmosphere at 0 to 5 °C. To this solution, the above lithium diisopropylamide solution was added dropwise over 30 minutes, and the mixture was further stirred at 5 to 20 °C for 16 hours.

In a separate vessel, 35 mL of 3 N-hydrochloric acid and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

35

The residue was purified by silica gel column

chromatography (Merck's Kieselgel 60, hexane:ethyl acetate = 2:1) to give 124 mg of tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate (yellow oil) in 6% yield.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz/ppm): 1.48 (9H, s), 2.668-2.83 (2H, m),  
5 3.0-3.8 (2H, bs), 3.42 (2H, s), 4.02-4.17 (2H, m), 4.40 (1H, m)

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 400 MHz/ppm): 27.8, 45.7, 51.0, 65.6, 68.0, 82.3, 166.4, 203.4

#### 10 Example 10 Tert-butyl (5S)-5,6-dihydroxy-3-oxohexanoate

Under argon gas, a solution composed of 3.90 g (38.5 mmol) of diisopropylamine and 3 mL of tetrahydrofuran was added dropwise to 22.9 mL (35 mmol) of n-butyllithium/hexane (1.5 mol/L) with stirring at 5 °C and the mixture was stirred for  
15 1 hour to prepare a lithium diisopropylamide solution.

In 3.0 mL of tetrahydrofuran were dissolved 1.02 g (10 mmol) of (3S)-3-hydroxybutyrolactone and 2.32 g (20 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 °C. To this solution was added 5.7 g (10  
20 mmol) of a solution of tert-butylmagnesium chloride in toluene/tetrahydrofuran (1:2.5, by weight) (1.75 mol/kg) dropwise over 10 minutes, and the mixture was further stirred at 5 °C for 50 minutes. Then, the lithium diisopropylamide solution prepared above was added dropwise over 30 minutes and  
25 the mixture was further stirred at 5 to 20 °C for 16 hours.

In a separate vessel, 30 mL of 3 N-hydrochloric acid and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous  
30 sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

The residue was purified by silica gel column chromatography (Merck's Kieselgel 60, hexane:ethyl acetate =  
35 2:1) to give 980 mg of tert-butyl (5S)-5,6-dihydroxy-3-

oxohexanoate (red oil) in 48% yield.

#### INDUSTRIAL APPLICABILITY

- 5 The present invention, constituted as described above, enables the production of 5-hydroxy-3-oxopentanoic acid derivatives, which are of use as pharmaceutical intermediates, particularly intermediates of HMG-CoA reductase inhibitors, from inexpensive, readily available starting compounds at a non-very-low temperature.

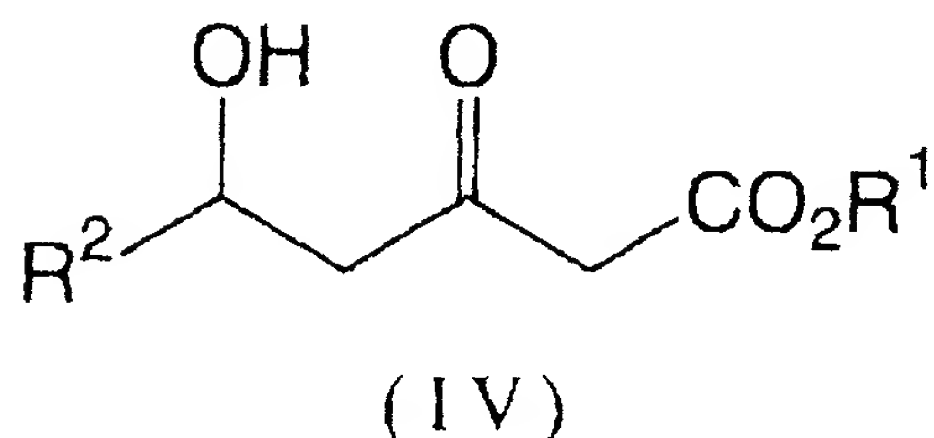
10

11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000

## CLAIMS

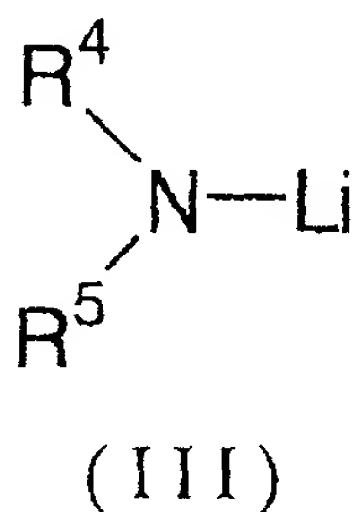
1. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):

5



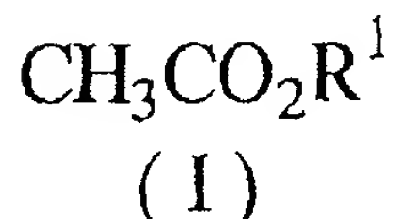
wherein  $\text{R}^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $\text{R}^2$  represents any of hydrogen, an  
 10 alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group  
 15 and an alkoxycarbonyl group,

which comprises permitting a lithium amide of the following formula (III):



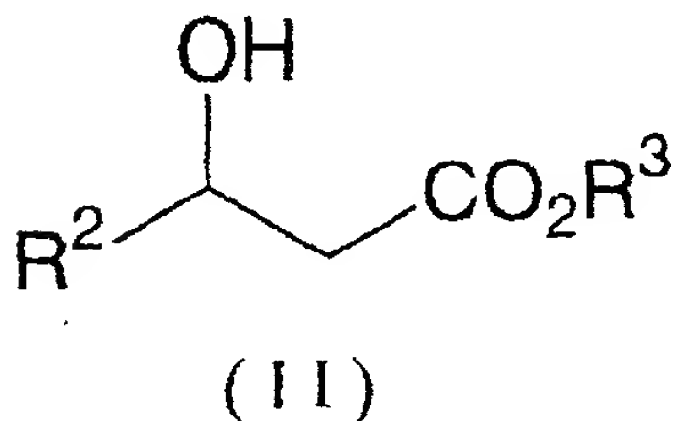
20 wherein  $\text{R}^4$  and  $\text{R}^5$  may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II) at a temperature not below  $-20^{\circ}\text{C}$ :



5

wherein  $\text{R}^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



10

15

20

wherein  $\text{R}^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group;  $\text{R}^3$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $\text{R}^2$  and  $\text{R}^3$  may be joined to each other to form a ring.

2. The process according to Claim 1

wherein, referring to the lithium amide,  $\text{R}^4$  and  $\text{R}^5$  each represents an isopropyl group.

25

3. The process according to Claim 1 or 2

wherein, referring to the acetic acid ester,  $\text{R}^1$

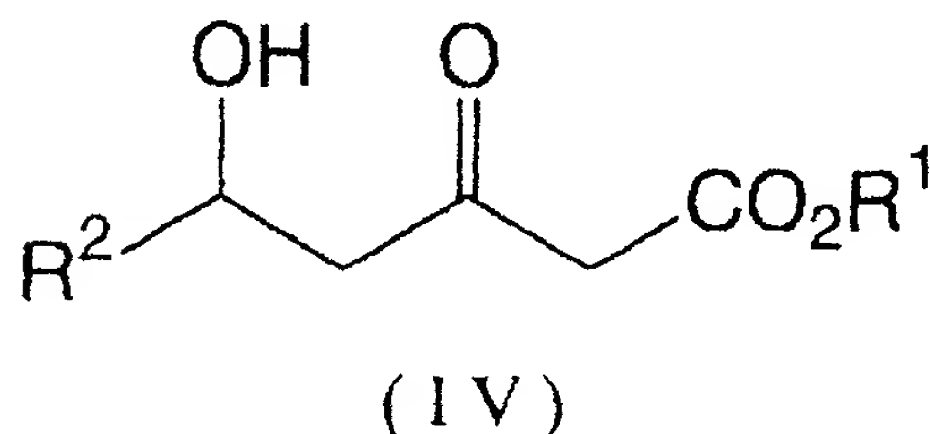
represents a tert-butyl group.

4. The process according to Claim 1, 2 or 3  
 wherein a magnesium halide is added in permitting the  
 5 lithium amide to act.

5. The process according to Claim 4  
 wherein magnesium chloride is used as the magnesium  
 halide.

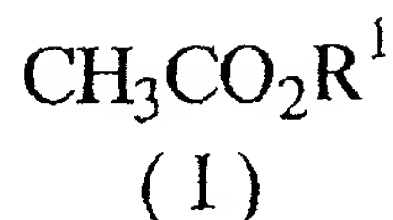
10

6. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



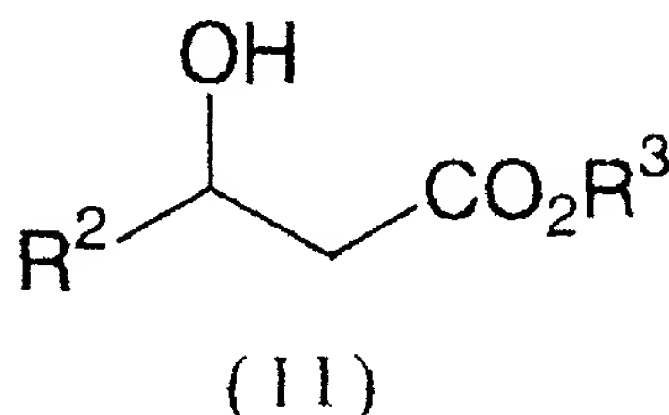
- 15 wherein R<sup>1</sup> represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R<sup>2</sup> represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent,  
 20 an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

- which comprises treating a mixture of an acetic acid ester  
 25 of the following formula (I) and a 3-hydroxypropionic acid derivative of the following formula (II):



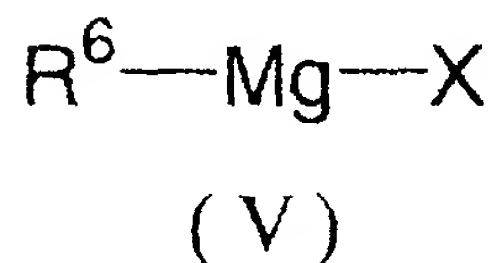
wherein  $\text{R}^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:

5



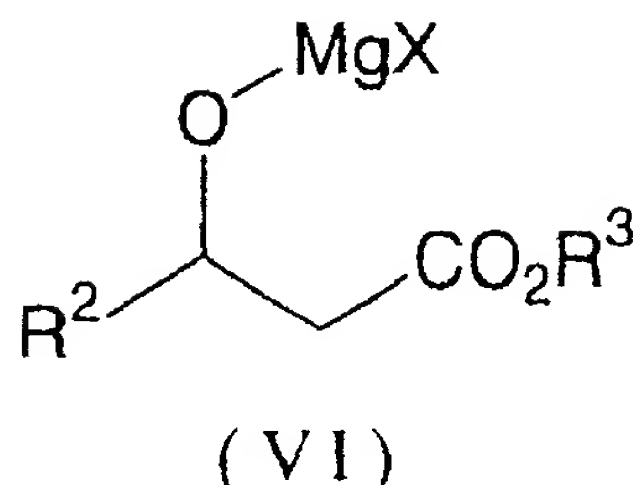
- wherein  $\text{R}^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group;  $\text{R}^3$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $\text{R}^2$  and  $\text{R}^3$  may be joined to each other to form a ring,

with a Grignard reagent of the following formula (V):



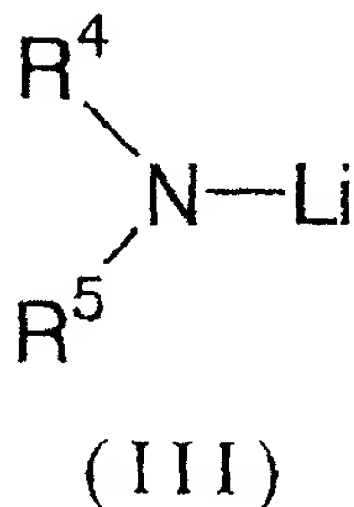
- wherein  $\text{R}^6$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and X represents halogen,
- to prepare a mixture of a compound of the following formula (VI) and an acetic acid ester of the above formula (I):





wherein  $\text{R}^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group;  $\text{R}^3$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms;  $\text{R}^2$  and  $\text{R}^3$  may be joined to each other to form a ring; and X represents a halogen atom,

and permitting a lithium amide of the following formula (III):



wherein  $\text{R}^4$  and  $\text{R}^5$  may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group

to act upon the mixture at a temperature not below  $-20^\circ\text{C}$ .

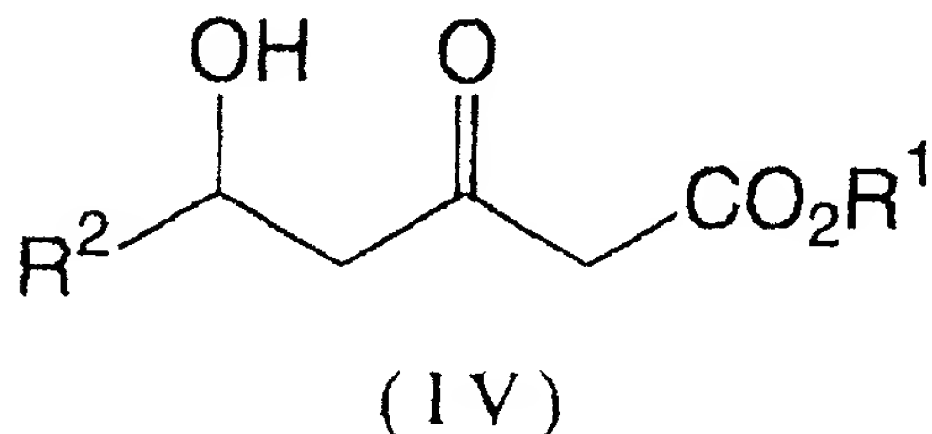
7. The process according to Claim 6

wherein, referring to the lithium amide,  $R^4$  and  $R^5$  each is an isopropyl group.

8. The process according to Claim 6 or 7  
 5 wherein, referring to the acetic acid ester,  $R^1$  represents a tert-butyl group.

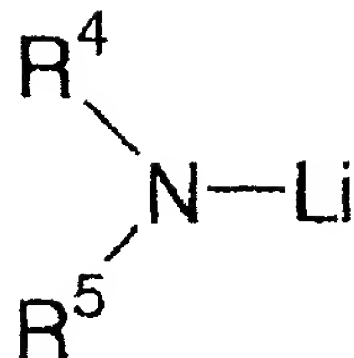
9. The process according to Claim 6, 7 or 8  
 10 wherein, referring to the Grignard reagent,  $R^6$  represents a tert-butyl group and X represents a chlorine atom.

10. A process for producing a 5-hydroxy-3-oxopentanoic acid derivative of the following formula (IV):



15 wherein  $R^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and  $R^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent,  
 20 an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent, a cyano group, a carboxyl group and an alkoxycarbonyl group,

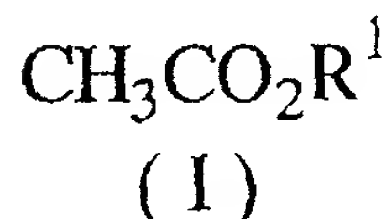
25 which comprises permitting a lithium amide of the following formula (III):



(III)

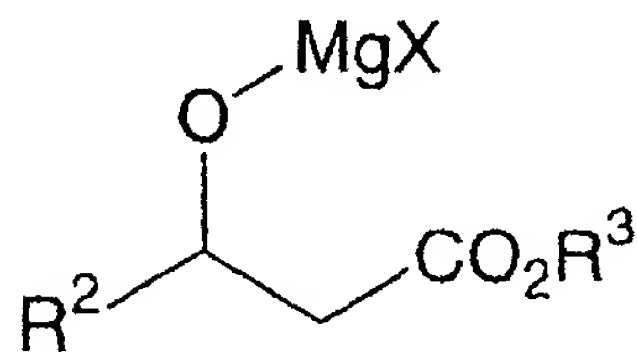
5 wherein  $\text{R}^4$  and  $\text{R}^5$  may be the same or different and each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

to act upon a mixture of an acetic acid ester of the following formula (I) and a compound of the following formula (VI) at a temperature not below  $-20^\circ\text{C}$ :



10

wherein  $\text{R}^1$  represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms:



(VI)

15

wherein  $\text{R}^2$  represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms which may have a substituent, an alkenyl group of 2 to 12 carbon atoms which may have a substituent, an aryl group of 6 to 12 carbon atoms which may have a substituent, an aralkyl group of 7 to 12 carbon atoms which may have a substituent,

20

a cyano group, a carboxyl group and an alkoxycarbonyl group;  
 $R^3$  represents any of an alkyl group of 1 to 12 carbon atoms,  
 an aryl group of 6 to 12 carbon atoms and an aralkyl group of  
 7 to 12 carbon atoms;  $R^2$  and  $R^3$  may be joined to each other to  
 5 form a ring; and X represents a halogen atom.

11. The process according to Claim 10  
 wherein, referring to the lithium amide,  $R^4$  and  $R^5$  each  
 represents an isopropyl group.

10

12. The process according to Claim 10 or 11  
 wherein, referring to the acetic acid ester,  $R^1$  represents  
 a tert-butyl group.

15

13. The process according to Claim 10, 11 or 12  
 wherein, referring to the compound (VI), X represents a  
 chlorine atom.

20

14. The process according to any of Claims 1 to 13  
 wherein  $R^3$  is a methyl group or an ethyl group.

15. The process according to any of Claims 1 to 14  
 wherein  $R^2$  is a chloromethyl group, a cyanomethyl group  
 or a benzyloxymethyl group.

25

16. The process according to any of Claims 1 to 13  
 wherein  $R^2$  and  $R^3$  are joined to each other to form a  
 methylene group.

30

17. The process according to any of Claims 1 to 16  
 wherein the compound (II) or (VI) is optically active.

## ABSTRACT

This invention provides a process for producing a 5-hydroxy-3-oxopentanoic acid, a useful pharmaceutical  
5 intermediate, easily from a readily available, inexpensive starting material without using any extraordinary production equipment such as a very-low-temperature reactor.

Thus, this invention provides a process for producing a 5-hydroxy-3-oxopentanoic acid

10 which comprises permitting a lithium amide to act upon a mixture of an acetic acid ester and a 3-hydroxypropionic acid derivative at not below  $-20^{\circ}\text{C}$ .

Further, this invention also provides a process for producing a 5-hydroxy-3-oxopentanoic acid

15 which comprises treating a mixture of an acetic acid ester and a 3-hydroxypropionic acid derivative with a Grignard reagent to prepare a mixture of a compound and an acetic acid ester of the above formula (I),

20 and permitting a lithium amide to act upon the mixture at a temperature not below  $-20^{\circ}\text{C}$ .

05 APR 2001

09/762215  
1581/00240

# DECLARATION FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

## Processes for the Preparation of 5-Hydroxy-3-Oxopentanoic Acid Derivatives

the specification of which (check one)

[ ] is attached hereto [XX] was filed on June 2, 2000, as United States Patent Application Serial No or PCT International Application Number PCT/IP00/03574, and was amended on 19 (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 CFR § 1.56(a)

Prior Foreign Application(s) I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application No.	Country	Day/Month/Year Filed	Priority Claimed
11/158033	Japan	4/June/1999	[XX] YES
2000/23804	Japan	1/February/2000	[XX] YES
			[ ] YES
			[ ] YES

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below or 34 U.S.C § 365(c) of any PCT International Application Designating the United States of America listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT application in the manner provided by 35 U.S.C. § 112, first paragraph, I acknowledge the duty to disclose material information as defined in 37 CFR § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(U.S. or PCT Application Serial No.)	(U.S. or PCT Filing Date)	(Status - patented, pending, abandoned)

I hereby appoint the following registered practitioners. George Vande Sande, Registration No. 17,276; Burton A. Amernick, Registration No. 24,852; Richard Wiener, Registration No. 18,741; Townsend M. Belser, Jr., Registration No. 22,956; Morris Liss, Registration No. 24,510; George R. Pettit, Registration No. 27,369; Elzbieta Chlopecka, Registration No. 32,767; William E. Curry, Registration No. 43,572; David W. Ward, Registration No. 45,198, and John A. Evans, Ph.D., Registration No. 44,100, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith

Send Correspondence and Direct Telephone Calls to  
Burton A. Amernick  
(202) 331-7111

Burton A. Amernick  
Pollock, Vande Sande & Amernick, R.L.L.P.  
P.O. Box 19088  
Washington, D.C. 20036-0088 U.S.A.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Akira Nishiyama

Inventor's Signature Akira Nishiyama Date MAR. 22. 2001  
Residence Address 1289-8, Nagasuna, Noguchicho, Kakogawa-shi, Hyogo 675-0016, Japan  
Citizenship Japan  
Post Office Address Same as above  
[XX] See next page for additional inventors

# DECLARATION FOR PATENT APPLICATION

## Page 2

Full name of second joint inventor (if any) Kenji Inoue

Inventor's Signature

Kenji Inoue

Date

MAR. 22. 2001

Residence Address

82-2-501, Awazu, Kakogawacho, Kakogawa-shi, Hyogo 675-0039, Japan

Citizenship

Japan

Post Office Address

Same as above

Full name of third joint inventor (if any) \_\_\_\_\_

Inventor's Signature

Date

Residence Address

Citizenship

Post Office Address

Full name of fourth joint inventor (if any) \_\_\_\_\_

Inventor's Signature

Date

Residence Address

Citizenship

Post Office Address

Full name of fifth joint inventor (if any) \_\_\_\_\_

Inventor's Signature

Date

Residence Address

Citizenship

Post Office Address

Full name of sixth joint inventor (if any) \_\_\_\_\_

Inventor's Signature

Date

Residence Address

Citizenship

Post Office Address

Full name of seventh joint inventor (if any) \_\_\_\_\_

Inventor's Signature

Date

Residence Address

Citizenship

Post Office Address

Full name of eighth joint inventor (if any) \_\_\_\_\_

Inventor's Signature

Date

Residence Address

Citizenship

Post Office Address